Visual snow syndrome: a review on diagnosis, pathophysiology, and treatment

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Abstract: PURPOSE OF REVIEW Visual snow is considered a disorder of central visual processing resulting in a perturbed perception of constant bilateral whole-visual field flickering or pixelation. When associated with additional visual symptoms, it is referred to as visual snow syndrome. Its pathophysiology remains elusive. This review highlights the visual snow literature focusing on recent clinical studies that add to our understanding of its clinical picture, pathophysiology, and treatment. RECENT FINDINGS Clinical characterization of visual snow syndrome is evolving, including a suggested modification of diagnostic criteria. Regarding pathophysiology, two recent studies tested the hypothesis of dysfunctional visual processing and occipital cortex hyperexcitability using electrophysiology. Likewise, advanced functional imaging shows promise to allow further insights into disease mechanisms. A retrospective study now provides Class IV evidence for a possible benefit of lamotrigine in a minority of patients. SUMMARY Scientific understanding of visual snow syndrome is growing. Major challenges remain the subjective nature of the disease, its overlap with migraine, and the lack of quantifiable outcome measures, which are necessary for clinical trials. In that context, refined perceptual assessment, objective electrophysiological parameters, as well as advanced functional brain imaging studies, are promising tools in the pipeline.

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Visual snow syndrome: a review on diagnosis, pathophysiology, and treatment

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Keywords
migraine, palinopsia, persistent visual phenomena, visual snow, visual static

INTRODUCTION

Since the first description of visual snow in the literature in 1995 [1], visual snow syndrome has emerged as a distinct clinical entity [2▪▪]. The hallmark of disease is the perception of constant bilateral whole-visual field flickering or pixelation, affecting the patients' daily life. *Visual snow syndrome* is defined as visual snow with at least two additional visual symptoms as outlined below. Symptom onset ranges from childhood [3,4] to elderly patients [5], but is usually reported in young adulthood, equally affecting men and women [6,7▪]. There is an ongoing debate as to whether visual snow syndrome should be considered as an organic disease or rather as a heightened perception of normal sensory phenomena [8]. However, the surprising stereotypy of patients describing their symptoms, even in the absence of previous knowledge about this condition, speaks against it being psychogenic in nature. Visual snow syndrome, by definition, is a benign condition and should not be associated with signs of a progressive ophthalmic or neurological disease. On rare occasions, however, visual snow symptoms have also been described in patients with serious neurological diseases such as Creutzfeldt-Jakob disease [9] or glycine receptor antibody syndrome [10]. The latter again seems to underpin a probable organic basis and emphasizes that careful adherence to diagnostic criteria, particularly the exclusion of other ophthalmic or neurologic disease, is essential.

Early studies have focused on clinical characterization of visual snow syndrome [11–14]. The pathophysiology, however, remains still unclear, which goes hand in hand with the lack of effective treatment strategies. This review follows up on a

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KEY POINTS

- Thorough clinical characterization of visual snow syndrome has led to its recognition as a clinical entity.
- The pathophysiology remains elusive; however, bilateral pan-visual field involvement, frequently associated palinopsia, abnormal suprathreshold processing of contrast and luminance, electrophysiological findings as well as functional brain imaging point towards dysfunctional central visual processing.
- Major challenges remain the purely subjective nature of visual snow syndrome, its overlap with migraine, and most importantly, the lack of quantifiable outcome measures, which are prerequisite to design prospective clinical trials.
- Based on a retrospective chart review, there is Class IV evidence that a minority of patients may profit from a trial of lamotrigine.
- The majority of patients copes well with reassurance about the benign nature of visual snow syndrome.

comprehensive review article about visual snow syndrome by Puledda *et al.* [2▪▪] published in February 2018 in this journal. Our article highlights the most recent literature on visual snow syndrome with a focus on the clinical studies that add to our understanding and management of the condition. The objective of this review is to condense our current appreciation of the clinical picture, of the pathophysiology and available treatments.

We did a systematic literature search on PubMed up to August 2019 for articles on visual snow with the keywords 'visual snow' 'visual snow syndrome', 'visual static', and 'persistent positive visual phenomena'.

VISUAL SNOW SYNDROME

The clinical picture

Based on their first systematic characterization of visual snow patients, preliminary criteria for visual snow syndrome were elaborated by Schankin *et al.* [11] and later suggested as definite clinical criteria [2▪▪]. These consist of

(1) Visual snow lasting longer than 3 months: perceived as dynamic, continuous, tiny dots in the entire visual field.
(2) At least two additional visual symptoms of the following four categories:
  (a) Palinopsia: afterimages or trailing of moving objects.
  (b) Enhanced entoptic phenomena (modification suggested by Metzler and Robertson [15▪]: 'other frequent or persistent visual phenomena'): excessive floaters in both eyes, excessive blue field entoptic phenomena, self-light of the eye, spontaneous photopsias.
  (c) Photophobia.
  (d) Nyctalopia.
(3) Symptoms are not consistent with typical migraine visual aura.
(4) Symptoms are not better explained by another disorder.

Metzler and Robertson [15▪] recently challenged these criteria, namely section B (ii) 'enhanced entoptic phenomena' based on the fact that they had difficulty applying this section in the clinic. Instead, they proposed B (ii) to be labelled 'other frequent or persistent visual phenomena' arguing that 'entoptic phenomena' are generally considered to be phenomena arising from structures within the eye. Apart from the fact that photopsias do not necessarily originate from within the eye [16], the proposed mild modification of the visual snow syndrome criteria would allow accounting for otherwise unclassifiable phenomena described by some patients with visual snow. The latter include 'halos around light-sources', 'geometric and coloured images that distort vision', 'metamorphopsias', 'straight lines moving across the visual field', 'water running down a window', and 'coloured clouds when closing eyes' [11].

Irrespective of this semantic debate, visual snow syndrome criteria base on purely subjective descriptions of visual symptoms. Ophthalmic and neurological examination is typically normal [11], including perimetry [5,12,13,17], optical coherence tomography [17], electroretinography [11–13,17] as well as – until recently – visual evoked potentials (VEP) [11–13,17].

On brain imaging, left occipital bending has been mentioned in 4/14 patients [18▪▪]. Two studies found this structural peculiarity to be more frequent in patients with major depressive disorders (35.3 vs. 12.3%) and with bipolar disorders (35.3 vs. 8.3%) compared with healthy controls. However, the clinical significance of this finding in patients with visual snow is unclear. Otherwise, structural MRI findings are typically reported normal [12,13].

Commonly associated nonvisual symptoms are comorbid migraine, tinnitus, impaired concentration, lethargy, anxiety, depression, balance disorder, and tremor [5,7▪,13,19▪▪]. Migraine clearly is the major confounding factor and thus challenges visual snow research. It is not only a very common

comorbid disease (up to 58% of visual snow patients) [13,14,19▪▪], but probably also shares common disease mechanisms with visual snow [11,14], which has been discussed in more detail by Puledda *et al.* [2▪▪].

Pathophysiology

Visual snow syndrome is generally considered to involve dysfunctional central visual processing [2▪▪,6,7▪,15▪,19▪▪]. However, its cause remains largely unknown.

Lauschke *et al.* [13] tested colourimetry in 12 visual snow patients and found the yellow-blue colour spectrum to provide relief of symptoms in 10/12 patients. Thus, they consider visual snow to be a disorder of central colour-dependent processing involving the magnocellular pathway and suggested thalamocortical dysrhythmia as a possible underlying mechanism. The latter disease concept has been mostly discussed in the context of neurogenic pain, tinnitus, Parkinson's disease, and depression [20–22]. While being an interesting hypothesis, studies actually measuring thalamocortical dysrhythmia in visual snow patients are regrettably still missing.

Chen *et al.* [23] mentioned cortical hyperexcitability as a possible pathophysiological mechanism based on a magnetoencephalography study involving six patients with 'persistent visual aura', two of which had visual snow.

More recently, the concept of cortical hyperexcitability was supported in a behavioural study by McKendrick *et al.* [24]. Consistent with elevated spontaneous neural firing in the primary visual cortex, they found abnormal suprathreshold processing of contrast (centre-surround contrast matching) and luminance (luminance increment detection in noise) in 16 visual snow patients compared with 18 controls. However, no differences were found for global form and motion tasks, which are attributed to extrastriate processing. If confirmed in larger studies, measurement of perceptual differences in visual snow may hold potential for diagnostic clinical tests and monitoring of treatment effects in the future.

Eren *et al.* [25▪▪] tested the hypothesis of dysfunctional visual processing using pattern-reversal VEP in 18 affected patients compared with 18 migraineurs and 18 healthy controls. On a group level, they found a trend for reduced N75-P100 amplitudes in visual snow patients and a mildly, but significantly increased N145 latency compared with healthy controls independent of comorbid migraine. The fusiform gyrus is the supposed origin of the late phase P100 [26] and is adjacent to the lingual gyrus. Arguing that late phase P100 represents the transition to N145, – which was prolonged in the study – the authors claim to possibly show the first electrophysiological correlate to the reported hypermetabolism of the lingual gyrus [14]. While the line of argument regarding localization seems rather long-winded, the findings of Eren *et al.* might still further support the idea of visual snow as a disorder involving extrastriate cortical areas [25▪▪]. Of note, latencies of N75 and P100 did not differ between visual snow and controls, making dysfunction of the early cortical visual processing unlikely. In addition, there was no statistically significant difference of N75-P100 amplitude habituation to repetitive VEP stimulation (six consecutive blocks of 75 responses) between groups.

Based on related previous case reports [27,28], Yildiz *et al.* [18▪▪] prospectively investigated occipital cortex hyperexcitability by measuring the habituation response to repetitive pattern-reversal VEP consisting of 10 blocks of 100 averaged responses. Ten visual snow patients with migraine (VS_m), seven visual snow patients without migraine (VS_{wom}), and 12 healthy controls were recruited. They measured the N75-P100 VEP amplitude ratios of the 10th/1st block of the right and left eye. Contrary to the results of Eren *et al.*, this study found a loss of the habituation response in VS_m and VS_{wom} compared with the expected habituation in healthy controls. There was no statistically significant difference between VS_m and VS_{wom}, meaning that presence or absence of migraine did not influence the habituation response. Lack of habituation has been considered a neurophysiological hallmark of interictal migraine. However, the latter has been put into question recently [29]. Unfortunately, the study by Yildiz *et al.* [18▪▪] did not include a pure migraine control group without visual snow. The authors also assessed transcranial magnetic stimulation phosphene detection and found a lower left phosphene threshold in patients with visual snow. In the post-hoc analysis, the latter difference only reached statistical significance in VS_m compared with healthy controls. In sum, Yildiz *et al.* propose loss of VEP habituation and decreased phosphene threshold as possible surrogate markers indicating occipital cortex hyperexcitability.

It is understood that objective electrophysiological parameters would be extremely useful to assay benefits of treatment in visual snow. At present, results of electrophysiological studies seem to be differing [11–13,17,18▪▪,25▪▪] which might, however, partly be related to different examination protocols, for example, when assessing habituation. Larger studies are awaited to elucidate the field.

Functional brain imaging studies seem most appropriate to find evidence for dysfunctional

central visual processing. Apart from the occasional occipital bending mentioned above, brain imaging studies usually do not show specific *structural* abnormalities [11–13]. Jager *et al.* [30] investigated cerebral water diffusion and perfusion on MRI and found no regional functional changes in his two patients with visual snow. Schankin *et al.* [14] investigated seventeen patients with visual snow using [(18) F]-2-fluoro-2-deoxy-D-glucose PET and found hypermetabolism of the right lingual gyrus and left anterior cerebellar lobe. This finding is consistent with a disorder allocated downstream of the primary visual cortex.

To further investigate abnormal central visual processing, we are currently analysing resting state functional MRI (fMRI) of patients with visual snow compared with healthy controls within, but also outside of the visual cortex. Preliminary data in ten patients with visual snow and ten healthy controls was presented at the 45th North-American Neuro-Ophthalmology Society Meeting in Las Vegas, USA, in March 2019 (https://www.nanosweb.org/files/Annual%20Meeting'/2019/FINAL%20-NANOS%20Brochure%20low%20res.pdf). Our results point towards functional hyperconnectivity in brain areas involved in form and motion processing, as well as in areas associated with attention and working memory. These findings suggest, that visual snow patients not only have a metabolically altered early visual cortex (lingual gyrus) [31], but also show functional abnormalities in brain areas associated with the accompanying symptoms of visual snow, such as palinopsia (unpublished data).

In an attempt to explain why visual snow is frequently associated with additional symptoms, Metzler and Robertson [15▪] discussed the concept of stochastic resonance, a nonlinear phenomenon where additional noise can improve the signal-to-noise ratio, thus lowering the detection threshold of another weak stimulus. The latter has not only been shown for stimuli involving the same sensory modality (e.g., vision) [32], but also for stimuli involving different senses (e.g., vision and hearing) [33]. The authors concluded that in a model of stochastic resonance, visual snow might, for example, enhance tinnitus or vice versa.

Patient management and treatment

Sharing our knowledge on visual snow and reassuring the patient about the benign nature of the condition often provides instant relief to the patient. Nevertheless, a minority of patients may request empiric treatment. Until recently, pharmacologic treatment was only based on case reports, small case series, or expert opinion [2▪▪,6,28,34]. Recently, van Dongen *et al.* [19▪▪] evaluated treatment options in a retrospective case series of 58 visual snow patients, out of which 47 patients had visual snow syndrome. Given the lack of evidence, 29 patients chose no drug treatment. None of the remaining treated patients experienced complete remission under medication. Lamotrigine (2×50 mg) was prescribed most frequently ($n = 26$) with partial remission of symptoms in 5/26 (19.2%). However, adverse events were reported in half of the patients (13/26) patients, including allergic reactions ($n = 3$) and excessive daytime sleepiness ($n = 1$). Eventually, only 4/26 patients continued lamotrigine treatment. One patient improved under topiramate ($n = 4$), but still stopped the medication because of side effects. Valproate ($n = 7$), acetazolamide ($n = 2$) and flunarizine ($n = 1$) did not improve symptoms in this case series. Overall, evidence for pharmacological treatment in visual snow remains scarce (Class IV evidence). Thus, treatment should be limited to selected patients only.

Treatment of comorbid diseases like migraine or mood disorders is certainly worth considering depending on the severity. However, there is no evidence suggesting benefit with regard to visual snow symptoms.

Recently, real-time fMRI neurofeedback has been proposed as a potential intervention for several neurological and psychiatric disorders [35–41]. As there is hypermetabolism in the lingual gyrus and growing evidence of dysfunctional connectivity in the brain, single region real-time fMRI neurofeedback may be a promising intervention strategy to normalize brain function in the future.

CONCLUSION

Research about visual snow syndrome has gone through an early phase of thorough clinical characterization leading to its recognition as a clinical entity. Overall, the disease is most likely related to dysfunctional central visual processing, which is also supported by the most recent clinical studies. Our scientific understanding of visual snow syndrome has started to grow as we now put bits and pieces of the puzzle together. However, major challenges remain, such as the purely subjective nature of visual snow syndrome, its overlap with migraine, and most importantly the lack of quantifiable and reliable outcome measures, which are prerequisite to design prospective clinical trials. In that context, measurement of refined perceptual differences, objective electrophysiological parameters, as well as advanced functional brain imaging studies including real-time fMRI neurofeedback, may hold

potential but need further investigations on a larger scale. In the meantime, we are left with Class IV evidence that a minority of patients may profit from a trial of oral lamotrigine and with the confidence that most patients cope very well with reassurance.

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Conflicts of interest

There are no conflicts of interest.

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